IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Fisher *et al.*		
Serial No.	:	09/907,907	Examiner :	Blanchard, D.
Filed	:	July 16, 2001	Group Art Unit:	1642
For	:	GENES DISPLAYING ENHANCED EXPRESSION DURING CELLULAR SENESCENCE AND TERMINAL CELL DIFFERENTIATION AND USES THEREOF		

DECLARATION OF DR. PAUL B. FISHER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

1. I, Dr. Paul B. Fisher, am an expert in cell biology, gene identification and cancer gene therapy. I currently am a Professor of Clinical Pathology and Director of Neuro-oncology with joint appointments in the Departments of Pathology, Urology and Neurosurgery and am the Michael and Stella Chernow Urological Cancer Research Scientist at the College of Physicians and Surgeons, Herbert Irving Comprehensive Cancer Center, Columbia University, New York, New York. I have a Ph.D. in cell biology, virology and somatic cell genetics. I have held academic positions for more than 20 years. I have as of the present time published more than 200 peer-reviewed articles in prestigious scientific journals, been commissioned to write several review articles and invited to deliver national and international seminars in my area of expertise. I am the recipient of several federally and privately funded research grants. I have served on scientific review committees for various Federal, private not-for-profit and international agencies including the National Institutes of Health, the CaPCure Foundation, The Samuel Waxman Cancer Research Foundation, The California Breast Cancer Research Foundation, The Dutch Cancer Research Society, the Italian Cancer Research Foundation etc. I hold a number of patents. A copy of my curriculum vitae is attached as Exhibit 1.

2. I am a co-inventor of the above-identified Patent Application.

3. The experiments described in the specification of the above-identified application were performed under my direction.

4. I understand that the Examiner has questioned whether mRNA levels of the claimed Old-35 gene correlate with protein expression and whether there is a correlation between an altered level of OLD-35 protein and a specific disease state. In response, I offer the following information based on findings of experiments performed under my supervision:

A. I would like to invite the Examiner's attention to EXHIBIT 2. The experimental data shown in EXHIBIT 2 demonstrates a correlation between the expression of Old-35 mRNA and OLD-35 protein.

Part A of the exhibit is a Northern blot performed by separating total cellular RNA derived from HO-1 human melanoma cells by electrophoresis and transferring the RNA onto a nylon membrane. Each lane represents a separate sample of RNA derived from distinct HO-1 cell populations not treated (Lane 0) or treated for 6, 12, 24, 36 and 48 hours with 1000 units of IFN-β in Lanes labeled 6, 12, 24, 36 and 48 respectively. A radioactively labeled Old-35 gene was used as probe to hybridize to Old-35 RNA molecules present on the membrane. Positive signals were detected by exposure to film which detect membrane-bound, radioactive, Old-35 gene-specific probe. The membrane was also hybridized to a control gene probe corresponding to the Glyceraldehyde-3-phosphate dehydrogenase gene (GAPDH) which demonstrates, by showing signals of equal intensity in all lanes, that each lane contains the same amount of total RNA.

Part B of EXHIBIT 2 is a Western Blot of total protein extract derived from HO-1 human melanoma cells gel-electrophoretically separated based on size of individual proteins in the extract. Following separation the proteins were transferred onto a nitrocellulose membrane. The transferred proteins were reacted with an antibody recognizing the OLD-35 protein. Positive signals, indicating presence of OLD-35 protein are detected by exposure to film utilizing a chemiluminesent detection method. Each lane represents a separate sample of protein derived from distinct HO-1 cell populations not treated (Lane 0) or treated for 6, 12, 24, 36 and 48 hours

with 1000 units of IFN-β in Lanes labeled 6, 12, 24, 36 and 48 respectively. The membrane is also utilized to detect EF1-α protein with an EF1-α specific antibody. By showing signals of approximately equal intensity in all lanes utilizing the EF1-α antibody, it is demonstrated that each lane contains the same amount of total protein.

As seen in EXHIBIT 2, part A, induction of the Old-35 gene occurs following treatment of HO-1 cells, a human metastatic melanoma derived cell-line, with Interferon-β as described in the specification. Robust gene expression at the RNA level is induced 6 h following Interferon-β treatment. There is very low undetectable level of Old-35 gene expression prior to treatment with the inducer, Interferon-β. Protein expression is visible at 6 h and peaks at 36h before a fall in level is seen at 48 h post-treatment with Interferon-β. The kinetics of RNA and protein expression is parallel and correlative since the peak level of protein induction clearly follows the peak levels of RNA induction and both follow similar induction kinetics. The difference in timing of peak levels and decay kinetics is because protein expression has to necessarily follow production of mRNA. Differences in the amplitude of signal is due to differences in half-life or relative stability of mRNA compared to protein and differences in the sensitivity of experimental procedure involving radioactive detection in part A and less sensitive chemiluminesent detection in part B. Therefore, there is indeed a parallel between expression of Old-35 mRNA and OLD-35 protein, in that there is a clear correlation between an increase in Old-35 mRNA expression and a proportional increase in OLD-35 protein levels within cells.

B. I would like to emphasize that the level of OLD-35 protein being analyzed and detected in EXHIBIT 2, part B is endogenous cellular protein. This demonstrates that any antibody used in similar experimental set-ups with similar recognition specificity would be able to detect OLD-35 protein and such results would be easily anticipated by persons skilled in the art based on the instant specification. In this regard I would also like to note that this application discloses a protein having amino acid sequence SEQ ID NO:42, which comprises amino acid residues 18-697 of the 783 amino acids comprising OLD-35 protein and in addition, containing nine additional residues at the C-terminus not found in the native OLD-35 protein. Based on my experience and the data presented in EXHIBIT 2, part B (a Western blot developed using an OLD-35 antibody to OLD-35 protein sequence residues 1-783), I believe that the antibody

generated against a protein having SEQ ID NO:42 would be extremely likely to recognize endogenous cellular OLD-35 protein, in that the nine foreign amino acid residues present therein and constituting less than two percent of the complete sequence, would not cause interference in the specificity of binding, and I further believe that the likelihood of generating an antibody directed exclusively toward these nine amino acids is low, given the low percentage of the protein they represent.

C. The experimental model utilized in the experiments in EXHIBIT 2, parts A and B, comprises in part, a human cell line called HO-1, derived from a human metastatic melanoma. This cell line has been demonstrated by several peer-reviewed research publications from my laboratory and others to be a suitable *in vitro* model for study of biochemical pathways and genes involved in growth arrest and reversible or terminal differentiation. Treatment of HO-1 with Interferon-β causes HO-1 cells to growth arrest. Therefore the data in EXHIBIT 2, parts A and B demonstrate that endogenous levels of both mRNA and protein expressed by the Old-35 gene change in parallel when cells undergo physiological changes such as growth arrest, differentiation or aging, so that detection of protein levels using the claimed antibodies would be useful in detecting such changes. Thus, an antibody of the invention would be useful in detecting growth arrest, differentiation or aging.

5. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of the Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this reissue application or any patent issued thereon.

Paul B. Fisher

Dr. Paul B. Fisher

Nov. 2, 2004

Date

BIOGRAPHICAL SKETCH

NAME	POSITION TITLE
Paul B. Fisher	**Professor**

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Hunter College of CUNY, NY	B.A.	1968	Biology / Chemistry
Herbert H. Lehman College of CUNY, NY	M.A.	1971	Genetics
Rutgers University, NJ	M.PH.	1973	Cell Biology, Virology
Waksman Institute of Microbiology	Ph.D.	1974	& Somatic Cell Genetics

Professional Experience:

1987-Present **Michael and Stella Chernow Urological Cancer Research Scientist,** Departments of Pathology and Urology, Columbia University, College of Physicians & Surgeons, NY, NY 10032
1987-Present **Adjunct Professor and Visiting Scholar,** New York University, NY, NY 10003
1988-Present **Director of Neuro-Oncology Research,** Department of Neurological Surgery, Columbia University, College of Physicians & Surgeons, NY, NY 10032
1991-Present **Professor of Clinical Pathology,** Department of Pathology, Columbia University, College of Physicians and Surgeons, NY, NY 10032

Editorial and Association Boards: Archives of AIDS Research (Associate Editor); Cancer Biology and Therapy (Editorial Board); Cancer Research (Associate Editor); In Vivo (Associate Editor); International Institute of Cancer Research (Scientific Advisory Board); International Journal of Oncology (Associate Editor); International Society of Cancer Gene Therapy (Council Member); International Society of Differentiation (Board of Directors); Journal Experimental Therapeutics & Oncology (Associate Editor); Journal Experimental & Clinical Cancer Research (Associate Editor); Mechanisms of Differentiation (Series Editor; CRC Press); Molecular & Cellular Differentiation (Editor-in-Chief; CRC Press); Urology (Expert Reviewer); **Consultantships**: Project and Site Visit Reviewer for Health Effects Division of DOE; Ad Hoc Reviewer Chemical Pathology Study Section; **Grant Reviewer**: NSF, NCI, DOE, New Jersey Commission on Cancer Research, California Breast Cancer Foundation and Ontario Ministry of Health, Canada.

Selected Publications (from a Total of 300):

1. Jiang, H., J. J. Lin, Z.-z. Su, N. I. Goldstein and P. B. Fisher. Subtraction hybridization identifies a novel melanoma differentiation associated gene, *mda-7*, modulated during human melanoma differentiation, growth and progression. *Oncogene* 11: 2477-2486, 1995.
2. Jiang, H., Z.-z. Su, J. J. Lin, N. I. Goldstein, C. S. H. Young and P.B. Fisher. The melanoma differentiation associated gene *mda-7* suppresses cancer cell growth. *Proc. Natl. Acad. Sci. USA* 93: 9160-9165, 1996.
3. Su, Z.-z., Y. Shi and P.B. Fisher. Subtraction hybridization identifies a progression elevated gene *PEG-3* with sequence homology to a growth arrest and DNA damage inducible gene. *Proc. Natl. Acad. Sci. USA* 94: 9125-9130, 1997.
4. Su, Z.-z., M.T. Madireddi, J.J. Lin, C.S.H. Young, S. Kitada, J.C. Reed, N.I. Goldstein and P.B. Fisher. The cancer growth suppressor gene *mda-7* selectively induces apoptosis in human breast cancer cells and inhibits tumor growth in nude mice. *Proc. Natl. Acad. Sci. USA* 95: 14400-14405, 1998.
5. Kang, D.-c., R. La France, Z.-z. Su and P.B. Fisher. Reciprocal subtraction differential RNA display (RSDD): an efficient and rapid procedure for isolating differentially expressed gene sequences. *Proc. Natl. Acad. Sci. USA* 95: 13788-13793, 1998.
6. Su, Z.-z., N.I. Goldstein, H. Jiang, M.-N. Wang, G.J. Duigou, C.S.H. Young and P.B. Fisher. *PEG-3*, a non-transforming progression gene, is a positive regulator of cancer aggressiveness and angiogenesis. *Proc. Natl. Acad. Sci. USA* 96: 15115-15120, 1998.
7. Huang, F., J. Adelman, H. Jiang, N.I. Goldstein and P.B. Fisher. Identification and temporal expression pattern of genes modulated during irreversible growth arrest and terminal differentiation in human melanoma cells. *Oncogene* 18: 3546-3552, 1999.
8. Huang, F., J. Adelman, H. Jiang, N.I. Goldstein and P. B. Fisher. Differentiation induction subtraction hybridization (DISH): an approach for cloning genes differentially expressed during growth arrest and terminal differentiation in human melanoma cells. *Gene* 236: 125-131, 1999.
9. Gopalkrishnan, R. V., K. A. Christiansen, N. I. Goldstein, R. A. DePinho and P. B. Fisher. Use of the human EF-1α promoter for expression can significantly increase success in establishing stable cell lines with consistent expression: a study using the tetracycline inducible system in human cancer cells. *Nucl. Acids Res.* 27: 4775-4782, 1999.
10. Madireddi, M. T., Su, Z.-z., C.S.H. Young, N.I. Goldstein and P.B. Fisher. *Mda-7*, a novel melanoma differentiation associated gene with promise for cancer gene therapy. *Adv. Exptl. Med. Biol.* 465: 239-261, 2000.
11. Madireddi, M.T., P. Dent and P.B. Fisher. Regulation of *mda-7* gene expression during human melanoma differentiation. *Oncogene* 19: 1362-1368, 2000.

12. Madireddi, M.T., P. Dent and P.B. Fisher. AP-1 and C/EBP transcription factors contribute to *mda-7* gene promoter activity during human melanoma differentiation. *J. Cell. Physiol.* 185: 36-46, 2000.
13. Jiang, H., D.-c. Kang, D. Alexandre and P. B. Fisher. RaSH, A rapid subtraction hybridization approach for identifying and cloning differentially expressed genes. *Proc. Natl. Acad. Sci. USA* 97: 12684-12689, 2000.
14. Su, Z.-z., Y. Shi and P. B. Fisher. Cooperation between AP1 and PEA3 sites within the progression elevated gene-3 (PEG-3) promoter regulate basal and differential expression of PEG-3 during progression of the oncogenic phenotype in transformed rat embryo cells. *Oncogene* 19: 3411-3421, 2000.
15. Kang, D.-c., H. Jiang, Q. Wu, S. Pestka and P. B. Fisher. Cloning and characterization of human ubiquitin-processing protease-43 from terminally differentiated human melanoma cells using a rapid subtraction hybridization protocol RaSH. *Gene* 267: 233-242, 2001.
16. Leszczyniecka, M., T. Roberts, P. Dent, S. Grant and P.B. Fisher. Differentiation therapy of cancer: basic science and clinical applications. *Pharmacology and Therapeutics* 90:105-156, 2001.
17. Mhashilkar, A. B., R. D. Schrock, M. Hindi, J. Liao, K. Sieger, F. Kourouma, X.H. Zou-Yang, E. Onishi, O. Takh, T. S. Vedvick, G. Fanger, L. Stewart, G. J. Watson, D. Snary, P. B. Fisher, T. Saeki, J. A. Roth, R. Ramesh and S. Chada. Melanoma differentiation associated gene-7 (*mda-7*): a novel anti-tumor gene for cancer gene therapy. *Mol. Med.* 7: 271-282, 2001.
18. Su, Z.-z., Y. Shi, R. Friedman, L. Qiao, D. Hinman, P. Dent and P. B. Fisher. PEA3 sites within the progression elevated gene-3 (PEG-3) promoter and mitogen activated protein kinase contribute to differential *PEG-3* expression in Ha-ras and v-raf oncogene transformed rat embryo fibroblast cells. *Nucl. Acids Res.* 29: 1661-1671, 2001.
19. Su, Z.-z., I.V. Lebedeva, R.V. Gopalkrishnan, N.I. Goldstein, C. A. Stein, J.C. Reed, P. Dent and P.B. Fisher. A combinatorial approach for selectively inducing programmed cell death in human pancreatic cancer cells. *Proc. Natl. Acad. Sci. USA* 98: 10332-10337, 2001.
20. Huang E. Y., M. T. Madireddi, R. V. Gopalkrishnan, M. Leszczyniecka, Z.-z. Su, I.V. Lebedeva, D.-c. Kang, H. Jiang, J. J. Lin, D. Alexandre, Y. Chen, N. Vozhilla, M. X. Mei, K. R. Christiansen, F. Sivo, N. I. Goldstein, A. B. Mhashilkar, S. Chada, E. Huberman, S. Pestka and P.B. Fisher. Genomic structure, chromosomal localization and expression profile of a novel melanoma differentiation associated (*mda-7*) gene with cancer specific growth suppressing and apoptosis inducing properties. Oncogene 20: 7051-7063, 2001.
21. Gopalkrishnan, R.V., D.-c. Kang and P.B. Fisher. Molecular markers and determinants of human prostate cancer metastasis. *J. Cell. Physiol.* 189: 245-256, 2001.
22. Pillutla, R.C., A.J. Blume, N.I. Goldstein and P.B. Fisher,. Target validation and drug discovery using genomic and display technologies. *Expert Opinion in Therapeutic Targets* 6: 517-532, 2002.
23. Lebedeva, I. V., Z.-z. Su, Y. Chang, S. Kitada, J. C. Reed and P. B. Fisher. The cancer growth suppressing gene *mda-7* induces apoptosis selectively in human melanoma cells. *Oncogene* 21: 708-718, 2002.
24. Su, Z.-z., R. V. Gopalkrishnan, G. Narayan, P. Dent and P. B. Fisher. Progression elevated gene-3, *PEG-3*, induces genomic instability in rodent and human tumor cells. *J. Cell. Physiol.* 192: 34-44, 2002.
25. Kang, D.-c., R. V. Gopalkrishnan, Q. Wu, E. Jankowsky, A. M. Pyle and P. B. Fisher. *Mda-5*, an interferon-inducible putative RNA helicase with dsRNA-dependent ATPase activity and melanoma growth suppressive properties. *Proc. Natl. Acad. Sci. USA* 99: 637-642, 2002.
26. Sarkar, D., Z.-z. Su, I.V. Lebedeva, M. Sauane, R.V. Gopalkrishnan, P. Dent and P.B. Fisher. *Mda-7* (IL-24): Signaling and functional roles. *BioTechniques, Oct. Suppl.*, 30-39, 2002.
27. Sarkar, D., Z.-z. Su, I.V. Lebedeva, M. Sauane, R.V. Gopalkrishnan, K. Valerie, P. Dent and P.B. Fisher. *mda-7* (IL-24) mediates selective apoptosis in human melanoma cells by inducing the coordinated overexpression of the GADD family of genes via p38 MAPK. *Proc. Natl. Acad. Sci. USA* 99: 10054-10059, 2002.
28. Leszczyniecka M., D.-c. Kang, Z.-z. Su and P. B. Fisher. Identification and cloning of *hPNPase*$^{old\text{-}35}$, human polynucleotide phosphorylase, in the context of terminal differentiation and cellular senescence. *Proc. Natl. Acad. Sci. USA* 99: 16636-16641, 2002.
29. Lebedeva, I.V., Z.-z. Su, D. Sarkar and P.B. Fisher. Restoring apoptosis as a strategy for cancer gene therapy: focus on p53 and *mda-7*. *Semin. Cancer Biol.* 13: 169-178, 2003.
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33. Su, Z.-z., Y. Chen, D.-c. Kang, W. Chao, M. Simm, D.J. Volsky and P.B. Fisher. Customized rapid subtraction hybridization (RaSH) gene microarrays identify overlapping expression changes in human fetal astrocytes resulting from HIV-1 infection or TNF-α treatment. Gene 306: 67-78, 2003.

34. Yacoub, A., C. Mitchell, A. Lister, I.V. Lebedeva, D. Sarkar, Z.-z. Su, C. Sigmon, R. McKinstry, V. Ramakrishnan, L. Qiao, W.C. Broaddus, R.V. Gopalkrishnan, S. Grant, P.B. Fisher and P. Dent. *mda*-7 (IL-24) inhibits growth and enhances radiosensitivity of glioma cells in vitro and in vivo. Clinical Cancer Res. 9: 3272-3281, 2003.
35. Lebedeva, I.V., Z.-z. Su, D. Sarkar, S. Kitada, P. Dent, S. Waxman, J.C. Reed and P.B. Fisher. Melanoma differentiation associated gene-7, *mda*-7/IL-24, promotes apoptosis in prostate cancer cells by promoting mitochondrial dysfunction and inducing reactive oxygen species. ***Cancer Res.*** 63: 8138-8144, 2003.
36. Fisher, P.B., R.V. Gopalkrishnan, S. Chada, R. Ramesh, E.A. Grimm, M.R. Rosenfeld, D.T. Curiel and P. Dent. *mda*-7/IL-24: A novel cancer selective apoptosis inducing cytokine gene: From the laboratory into the clinic. ***Cancer Biol. Therapy*** 2: S23-S37, 2003.
37. Dent, P., A. Yacoub, P.B. Fisher, M.P. Hagan and S. Grant. MAPK pathways in radiation responses. Oncogene 22: 5885-5896, 2003.
38. Sauane, M., R.V. Gopalkrishnan, I.V. Lebedeva, M.X. Mei, D. Sarkar, Z.-z. Su, D.-c. Kang, P. Dent, S. Pestka and P.B. Fisher. *Mda*-7/IL-24 induces apoptosis of diverse cancer cell lines through JAK/STAT-independent pathways. J. Cell Physiol. 196: 334-345, 2003.
39. Su, Z.-z., I.V. Lebedeva, D. Sarkar, R.V. Gopalkrishnan, C. Sigmon, A. Yacoub, K. Valerie, P. Dent and P.B. Fisher. Melanoma differentiation associated gene-7, *mda*-7/IL-24, selectively induces growth suppression, apoptosis and radiosensitization in malignant gliomas in a p53-independent manner. Oncogene 22: 1164-1180, 2003.
40. Yacoub, A., C. Mitchell, I.V. Levedeva, D. Sarkar, Z.-z. Su, R. McKinstry, R. V. Gopalkrishnan, S. Grant, P.B. Fisher and P. Dent. *mda*-7 (IL-24) inhibits growth and enhances radiosensitivity of glioma cells in vitro via JNK signaling. Cancer Biol. & Therapy 2: 347-353, 2003.
41. Lebedeva, I.V., D. Sarkar, Z.-z. Su, S. Kitada, P. Dent, C.A. Stein, J.C. Reed and P.B. Fisher. Bcl-2 and Bcl-x_L differentially protect human prostate cancer cells from induction of apoptosis by melanoma differentiation associated gene-7, *mda*-7/IL-24. Oncogene 22: 8758-8773.
42. Lebedeva, I.V., Z.-z. Su, D. Sarkar, S. Kitada, P. Dent, S. Waxman, J.C. Reed and P.B. Fisher. Melanoma differentiation associated gene-7, *mda*-7/IL-24, promotes apoptosis in prostate cancer cells by promoting mitochondrial dysfunction and inducing reactive oxygen species. Cancer Res. 63: 8138-8144, 2003.
43. Kang, D.-c., R. V. Gopalkrishnan, L. Lin, K. Valerie, S. Pestka and P.B. Fisher. Expression analysis and genomic characterization of human melanoma differentiation associated gene-5, *mda*-5: a novel type I interferon apoptosis-inducing gene. Oncogene, 23:1789-1800, 2004.
44. Gopalkrishnan, R.V., M. Sauane and P.B. Fisher. Cytokine and tumor cell apoptosis inducing selectivity of *mda*-7/IL-24. Intl. Immunopharmacology 4:635-647, 2004.
45. Sauane, M., R.V. Gopalkrishnan, H.-t. Choo, P. Gupta, I. V. Lebedeva, A. Yacoub, P. Dent and P.B. Fisher. Mechanistic aspects of *mda*-7/IL-24 cancer cell selectivity analyzed via a bacterial fusion protein. Oncogene, 23: 7679-7690, 2004.
46. Sarkar, D., D.-c. Kang, N.I. Goldstein and P.B. Fisher. Approaches for gene discovery and methods for defining novel protein interactions and networks. Functional Genomics, 5:231-244, 2004.
47. Pestka, S., C. D. Krause, D. Sarkar, M. R. Walter, Y. Shi and P.B. Fisher. Interleukin-10 and related cytokines and receptors. Annu. Rev. Immunol., 22:929-979, 2004.

Research Projects Active and Completed During the Last 3 Years:

"Analysis of Progression of the Transformed Phenotype" (Active)

Principal Investigator: Fisher, P.B.
Type/Grant No.: 1 R01 CA35675-19
Funding Agency: NIH/NCI
Period: 04/01/84 to 11/30/07

Determine the functional significance of a novel gene progression elevated gene-3 (PEG-3) in cancer progression.

"Mda-7: Novel Cancer Therapeutic Gene" (Active)

Principal Investigator: Fisher, P.B.
Type/Grant No.: 1 R01 CA97318-03
Funding Agency: NIH/NCI
Period: 10/01/02 to 9/30/07

Mechanism of action of the novel cancer-specific apoptosis-inducing gene *mda*-7/IL-24. This project focuses on the role of *mda*-7/IL-24 in inducing apoptosis selectively in melanoma with emphasis on interacting proteins and the role of cell surface receptors in mediating *mda*-7 activity.

"Novel Approaches for Pancreatic Cancer Therapy" (Active)

Principal Investigator: Fisher, P. B.
Type/Grant No.: 1 R01 CA098712-02
Funding Agency: NIH/NCI
1/21/03 to 1/01/08

The present studies are designed to mechanistically evaluate novel combinatorial therapeutic approaches for human pancreatic cancer and to develop new replicating viral vectors that can specifically and selectively target pancreatic cancer cells for destruction.

"Molecular Mechanisms of HIV-1 Mediated Encephalopathy" (Active)

Principal Investigator: Volsky, D.J.
Type/Grant No.: 1 P01 NS31492-11
Funding Agency: NIH/NS
Period: 05/01/98 to 08/31/08

The major goals of this project are to determine the role of a novel gene astrocyte elevated gene-1 (*AEG*-1) and glutamate transport in HIV-induced neuropathy. Studies will also focus on defining factors that can modulate the activity of the EAAT2 transporter in astorocytes . Program director for project 2 of this Program Project Grant.

"*Mda*-5: Novel Apoptosis Inducing Gene" (Active)

Principal Investigator: Fisher, P.B.
Type/Grant No.: 1 R01 GM068448-01
Funding Agency: NIH/GM
Period: 08/01/04 to 07/31/08

The major goals of this grant are to define the mechanism of action of a novel virus and interferon inducible gene, *mda*-5, which contains both a caspase recruitment domain (CARD) and a putative RNA helicase domain and can induce apoptosis.

"Exploiting Defects in Molecular Circuitry to Selectively Kill Pancreatic Cancer Cells" (Active)

Principal Investigator: Fisher, P.B.
Type/Grant No.: LF04-071
Funding Agency: Lustgarten Foundation for Pancreatic Cancer Research
Period: 1/7/04 to 12/31/04

These studies were designed to evaluate in animal models a novel conditionally replicating adenovirus that replicates only in pancreatic cancer cells, while simultaneously expressing interferon gamma.

"Novel Prostate Cancer Gene and Monoclonal Antibody" (Completed)

Principal Investigator: Fisher, P.B.
Type/Grant No.: 1 R01 CA74468-05
Funding Agency: NIH/NCI
Period: 08/20/98 to 06/30/04

The major goals of this grant are to determine the functional and translational potential of prostate carcinoma tumor antigen gene-1 (PCTA-1) and a novel monoclonal antibody in human prostate cancer.

"Strategies for Selectively Eradicating Prostate Cancer Cells" (Completed)

Principal Investigator: Fisher, P.B.
Type/Grant No.: DAMD-02-1-0041-01
Funding Agency: Army, DOD
Period: 03/04/02 to 06/01/04

The major goals of this project are to develop replication incompetent adenoviruses using the *PEG*-promoter to regulate expression of immune regulating genes in the context of prostate cancer. No overlap with the current project.

"Targeted Therapy of Human Breast Cancer" (Completed)

Principal Investigator: Fisher, P.B.
Type/Grant No.: R21 CA87170-02
Funding Agency: NIH/NCI
Period: 06/01/01 to 05/31/03

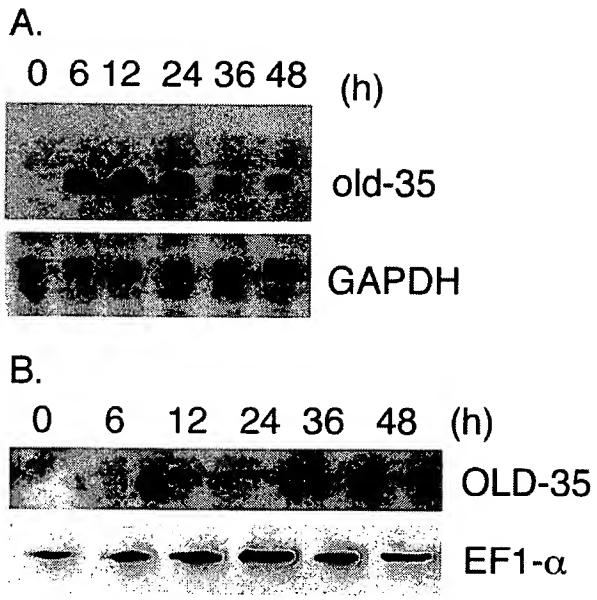
The major goals of this project are to develop replication incompetent adenoviruses using the PEG-promoter to regulate gene expression in the context of breast cancer.

"Enhancing the Antitumor Effects of a Cancer Suppressor Gene in Colorectal Cancers" (Completed)

Principal Investigator: Fisher, P.B.
Type/Grant No.: Sponsored Research Agreement
Funding Agency: Introgen Therapeutics Inc.
Period: 05/01/02 to 04/30/03

The goal of this project is to develop approaches for enhancing the antitumor activity of tumor suppressor genes toward colorectal cancer cells. No overlap exists with the current project.

Exhibit 2



Treatment with interferon (IFN)-β induces *hPNPase*$^{old-35}$ both at mRNA and protein levels. HO-1 cells were treated with 1000 units of IFN-β for the indicated time points and analyzed for *hPNPase*$^{old-35}$ mRNA and protein expression by Northern (A) and Western (B) blot analyses, respectively. GAPDH and EF1-α were used as loading controls.

BAKER BOTTS L.L.P.

04 FEB -2 PM 2:41

TO

In Re:	**Fisher et al.**		09/907,907
	(Applicant)		(Serial No.)
			A34584-A-PCT-USA
In Re:	**Information***	12/30/03	(070050.1664)
	(Title of Paper)	(Date)	(File No.)

The stamp of the Patent Office Mail Room hereon acknowledges the receipt of the above-identified papers on the date indicated by such stamp.

*1) Information Disclosure Statement (13 pages + copy); 2) PTO 1449 form with 105 references in three (3) bound volumes; and 3) Return Receipt Postcard.